AMENDMENTS

In response to the Examiner's Objections, Claim 7 has been amended to correct a minor typographical error. Claims 7 and 12 have been amended. Claims 22-24 were also added.

IN THE CLAIMS:

7. (First Amended) A method for expressing an increased number of B7 molecules on the surface of an antigen presenting cell to [more efficiently potentiate] enhance or regulate [the] an immune system comprising the steps of:

obtaining an upregulating agent;

administering the upregulating agent to an organism; and,

allowing an upregulation of B7 molecules on a cell whereby an expression of the B7 molecules allows reaction with an effector cell, the reaction with the armed effector cell potentiating an immune response.[.]

12. The method of Claim 7 wherein the B7 molecule is selected from the group comprising B7.1 [, B7,2 and B7.3], B7.2, B7h, B7-H1, B7-DC, and B7-H3.

22. The method of Claim 7, wherein the glucan containing composition at least comprises β 1,3-glucans.

23. The method of Claim 22, wherein the glucan containing composition further comprises β 1,6-glucans.

24. The method of Claim 7, wherein the glucan-containing composition is primarily comprised of microparticulate β glucan.

Claim Objection

The Examiner objected to Claim 7 because there were two (2) periods at the end of the sentence. This has been corrected by amending the Claim.

Restriction Requirement

In response to a restriction requirement, Applicants previously elected to prosecute Claims 7-17. Claims 1-6, and 18-21 are therefore cancelled.

Claims Rejection - 35 U.S.C. § 103(a):

Claims 7-17 are rejected under 35 U.S.C. § 103(a) as being obvious and being unpatentable over a non-patent document by Costello et al. entitled "Regulation of CD80/B7-1 and CD86/B7-2 molecule expression in human primary acute myeloid leukemia and their role in allogenic immune recognition," published in the European Journal of Immunology.

Applicants respectfully traverse the Examiner's rejection based upon Costello et al. because Applicants' invention is distinguishable from Costello in several ways. The Costello et al. paper describes an investigation into the role of B7 co-stimulatory molecules on the surface of human acute myelogenous leukemia (AML) cells in the induction of allogeneic CD4 T lymphocyte responses. Importantly, AML of the myelo/monocytic subtype is a cancer of antigen presenting cells (APC), and one of the proposed therapeutic approaches to this cancer is to use an allogeneic bone marrow transplant (a transplant of bone marrow from an individual genetically different from the patient with the AML) to provide allogeneic T-lymphocytes from the donor that can attack and kill the recipients AML cells. Since the amount of cell surface B7 is different on tumors cells from different AML patients, Costello et al. wanted to know the importance of B7 molecules on the AML cells in the activation of allogeneic CD4 T-lymphocytes. The approach they used was to employ the well-known ability of the endogenous cell surface molecule CD40L to induce B7 expression on APC bearing the CD40 receptor (see Banchereau et al., The CD40

antigen and its ligand, Annu. Rev. Immunol., 12:881-992, 1994). To do this, the authors either treated T-cells with interferon gamma (IFN-g) to induce CD40L expression, or transfected human L-cells with the gene for CD40L. They then co-cultivated either the T-cells or the genetically engineered L-cells with AML cells bearing CD40 in order to up-regulate the surface expression of B7 molecules on the AML cells. The conclusion of these authors was that B7 expression on AML cells correlates with the ability of these cancer cells to activate allogeneic T cell responses, although not all of the T cell responses they measured were stimulated.

The Costello et al. publication differs from our invention in the following ways: Costello et al. used an *in vitro* co-cultivation system and the widely known and published interaction of endogenous (external) cell surface proteins (CD40:CD40L) to increase the number of B7 molecules on AML cancer cells. In contrast, Applicants use a non-protein based substance, i.e., beta-1, 3-glucan, as a novel and unobvious way to stimulate or up-regulate the surface expression of B7 molecules on APC.

Further, the Costello authors were investigating the role of these co-stimulatory molecules in the activation of allogeneic T-lymphocytes, which are normal, and from healthy and genetically different donors for the purpose of enhancing allogeneic bone marrow transplant therapy. The Costello et al. paper is specific for and teaches that B7 molecules are needed on the surface of AML cells for stimulating some, but not all, allogeneic T cell responses (e.g., responses by T cells from genetically different individuals).

Unlike Applicants' invention and patent application, Costello et al. neither describes nor purports to have discovered a novel means of up-regulating the expression of B7

molecules on APC. Additionally, as an aside, while Costello et al. purport to describe interferon gamma (IFN-g) as a substance that can mediate up-regulation, it is known that IFN-g requires additional counterparts, components, and/or stimuli to upregulate the surface expression of B7 molecules (e.g. CD40L). Applicants' discovery, however, merely requires the use of beta glucan to cause up-regulation of B7 molecules on APC.

The Patent Examiner further rejected Applicants' claims on the basis that the Costello et al. paper purportedly teaches, *"expression of B7 molecules by antigen presenting cells provides stimulatory signals to T lymphocytes."* The fact that B7 molecules on APC provide co-stimulatory signals to T-lymphocytes is a fact that has been known for years, as indicated in the large number of publications referenced in Applicants' patent application. Applicants do not claim to have discovered this important relationship, *but rather* Applicants have invented a new, novel, and unobvious immunopharmacologic means of up-regulating the expression of these very important B7 molecules on APC.

Applicants specifically disclose a new and novel immunopharmacologic agent in their patent application that can be administered as an exogenous (external) material to an animal or human for the purpose of enhancing the expression of B7 family molecules on the surface of normal APC (e.g., macrophages). Importantly, someone having ordinary skill in the art, having read the Costello et al. paper, could not conceivably know that a β-1,3 glucan-containing composition, as provided by Applicants' invention, could be used for this purpose. There is no reference anywhere in the Costello et al. publication or in any of its cited references that would suggest that a β-1,3 glucan-containing composition could up-regulate the expression of B7 family molecules on normal APC.

In view of the teachings of the Costello et al. publication, Applicants respectfully submit that the Examiner's rejection of Applicants claims is improper. Rather, "[t]he consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art." *See In re O'Farrell*, 853 F.2d 894, 903 (Fed.Cir.1988), *citing Burlington Industries v. Quigg*, 822 F.2d 1581, 1583, 3 USPQ2d 1436, 1438 (Fed.Cir.1987). In fact, **both** the "suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chemical Co.*, 837 F.2d at 473, 5 USPQ2d at 1532. *It is not.* Therefore, Applicants respectfully submit that the Examiner has not made a prima facie showing of obviousness. *See In re O'Farrell*, 853 F.2d at 903; *In re Herschler*, 591 F.2d 693 (CCPA 1979).

The Patent Examiner also states that, "*it would have been obvious to one having ordinary skill in the art to utilize agents which are* ***known*** *[emphasis added] to up-regulate B7 molecules in order to increase the immune system.*" However, Applicants respectfully submit that their patent application discloses and identifies for the first time β-1,3 glucan-containing compositions as immunopharmacologic agents capable of up-regulating the expression of B7 molecules on APC. Until Applicants' important discovery, *it was not* known that β-1,3 glucan-containing compositions had such capability. *While Applicants do not claim to have discovered the first or the only immunopharmacologic means of up-regulating the expression of B7 family molecules on APC,* Applicants have conceived a novel and unobvious immunopharmacologic means of enhancing adaptive immune

responses by up-regulating B7 family molecules on APC. Moreover, according to the Federal Circuit:

> The admonition that "obvious to try" is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. *E.g., In re Geiger*, 815 F.2d at 686, 2 USPQ2d at 1278; *Novo Industri A/S v. Travenol Laboratories, Inc.*, 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir.1982); *In re Yates*, 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); *In re Antonie*, 559 F.2d at 621, 195 USPQ at 8-9. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1532 (Fed.Cir.1988); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380, 231 USPQ 81, 90-91 (Fed.Cir.1986), *cert. denied*, --- U.S. ----, 107 S.Ct. 1606, 94 L.Ed.2d 792 (1987); *In re Tomlinson*, 363 F.2d 928, 931, 150 USPQ 623, 626 (CCPA 1966).

In short, there is no teaching, much less suggestion in Costello et al., to use β-1,3 glucan-containing compositions to enhance immune responses by up-regulating B7 family molecules on APC.

In summary, Applicants' invention is not obvious in view of Costello et al. or any other publication cited therein by the mere fact that they may mention as the Examiner states, *"the up-regulation of B7 molecules by an up-regulating molecule"*. Instead, what Applicants claim as their invention is that β-1,3 glucan-containing compositions are novel and unobvious immunopharmacologic means of enhancing adaptive immune responses by

up-regulating B7 family molecules on APC. Furthermore, since the cited prior art does not provide any impetus to do what Applicants have done, Applicants respectfully traverse the Examiner's rejections under § 103 since the Examiner has not made a prima facie showing of obviousness. *In re Herschler*, 591 F.2d 693.

Conclusion

For the reasons submitted, the Applicants respectfully submit that the original, amended, and added claims are now proper, and that all claims are definite and define novel structure and function, which is alsc unobvious. Further, these amended claims now place this Application in condition for allowance. If the Examiner is of the opinion that the claims are not in condition for allowance then the Examiner is respectfully encouraged to contact the undersigned in order that this Application can be placed in allowable condition as soon as possible and without the need for further proceedings.

Also if the Examiner believes any additional fees are due, then the fees should be withdrawn from USPTO Deposit Account Number 13-2166.

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Date

Sincerely,
The Matthews Firm

Shirley A. Kopecky
Reg., No. 48,460
1900 West Loop South, Ste. 1800
Houston, Texas 77027
(713) 355-4200 Telephone
(713) 355-9689 Facsimile